The Oncologist®

Cancer Diagnostics and Molecular Pathology

Pathogenic *DPYD* Variants and Treatment-Related Mortality in Patients Receiving Fluoropyrimidine Chemotherapy: A Systematic Review and Meta-Analysis

Bhavina B. Sharma,[a,†] Karan Rai,[b,†] Heather Blunt,[c] Wenyan Zhao,[d] Tor D. Tosteson,[d,e] Gabriel A. Brooks[a,e]

[a]Dartmouth-Hitchcock Medical Center, Lebanon, New Hampshire, USA; [b]Geisel School of Medicine at Dartmouth, Lebanon, New Hamphsire, USA; [c]Biomedical Libraries, Dartmouth College, Hanover, New Hampshire, USA; [d]Department of Biomedical Data Science and [e]The Dartmouth Institute for Health Policy and Clinical Practice, Geisel School of Medicine, Lebanon, New Hampshire, USA

[†]Contributed equally

Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. 5-fluorouracil • Capecitabine • *DPYD* • Dihydropyrimidine dehydrogenase deficiency • Pharmacogenomics

Abstract

Background. Pathogenic variants of the *DPYD* gene are strongly associated with grade ≥3 toxicity during fluoropyrimidine chemotherapy. We conducted a systematic review and meta-analysis to estimate the risk of treatment-related death associated with *DPYD* gene variants.

Materials and Methods. We searched for reports published prior to September 17, 2020, that described patients receiving standard-dose fluoropyrimidine chemotherapy (5-fluorouracil or capecitabine) who had baseline testing for at least one of four pathogenic *DPYD* variants (c.1129-5923C>G [*HapB3*], c.1679T>G [**13*], c.1905+1G>A [**2A*], and c.2846A>T) and were assessed for toxicity. Two reviewers assessed studies for inclusion and extracted study-level data. The primary outcome was the relative risk of treatment-related mortality for *DPYD* variant carriers versus noncarriers; we performed data synthesis using a Mantel-Haenszel fixed effects model.

Results. Of the 2,923 references screened, 35 studies involving 13,929 patients were included. *DPYD* variants (heterozygous or homozygous) were identified in 566 patients (4.1%). There were 14 treatment-related deaths in 13,363 patients without identified *DPYD* variants (treatment-related mortality, 0.1%; 95% confidence interval [CI], 0.1–0.2) and 13 treatment-related deaths in 566 patients with any of the four *DPYD* variants (treatment-related mortality, 2.3%; 95% CI, 1.3%–3.9%). Carriers of pathogenic *DPYD* gene variants had a 25.6 times increased risk of treatment-related death (95% CI, 12.1–53.9; $p < .001$). After excluding carriers of the more common but less deleterious c.1129-5923C>G variant, carriers of c.1679T>G, c.1905+1G>A, and/or c.2846A>T had treatment-related mortality of 3.7%.

Conclusion. Patients with pathogenic *DPYD* gene variants who receive standard-dose fluoropyrimidine chemotherapy have greatly increased risk for treatment-related death. ***The Oncologist*** 2021;26:1008–1016

Implications for Practice: The syndrome of dihydropyrimidine dehydrogenase (DPD) deficiency is an uncommon but well-described cause of severe toxicity related to fluoropyrimidine chemotherapy agents (5-fluorouracil and capecitabine). Patients with latent DPD deficiency can be identified preemptively with genotyping of the *DPYD* gene, or with measurement of the plasma uracil concentration. In this systematic review and meta-analysis, the authors study the rare outcome of treatment-related death after fluoropyrimidine chemotherapy. *DPYD* gene variants associated with DPD deficiency were linked to a 25.6 times increased risk of fluoropyrimidine-related mortality. These findings support the clinical utility of *DPYD* genotyping as a screening test for DPD deficiency.

Correspondence: Gabriel A. Brooks, M.D., 1 Medical Center Drive, Lebanon, New Hampshire 03756, USA. Telephone: 603-650-7854; e-mail: gabriel.a.brooks@hitchcock.org Received March 30, 2021; accepted for publication August 6, 2021; published Online First on September 29, 2021. http://dx.doi.org/10.1002/onco.13967

Introduction

Fluoropyrimidine chemotherapy drugs, including 5-fluorouracil and its oral prodrug capecitabine, play an essential role in the treatment of gastrointestinal, breast, and head and neck cancers. Toxicities of fluoropyrimidine chemotherapies are well-described, and include neutropenia, mucositis, diarrhea, and hand-foot syndrome. Although changes in the administration and dosing of fluoropyrimidines have led to reductions in treatment-related toxicity in recent decades, approximately 15%–20% of patients receiving fluoropyrimidine monotherapy will have severe drug-related adverse effects (grade 3 or higher) during the course of treatment [1, 2]. Grade ≥3 toxicities are still more common among patients receiving fluoropyrimidine-based combination chemotherapy, affecting up to 56% of patients [3]. Treatment-related deaths (grade 5 toxic events) are rare during fluoropyrimidine-based chemotherapy, occurring in less than 1% of patients [3–5]. However, uncommon variants of the *DPYD* gene are increasingly recognized as a significant cause of severe and sometimes fatal fluoropyrimidine toxicity [6, 7].

The *DPYD* gene encodes dihydropyrimidine dehydrogenase (DPD), the rate-limiting enzyme in fluoropyrimidine metabolism, and deficiency of DPD enzymatic function leads to toxic accumulation of fluoropyrimidine metabolites [6, 8]. Germline variants in *DPYD* are the predominant cause of DPD deficiency, and pathogenic *DPYD* variants have been linked to a 5–8 times increased odds of grade 3 or higher toxicity [9, 10]. At least four *DPYD* alleles are widely recognized for their association with severe toxicity, including c.1129-5923 C>G (*HapB3*), c.1679T>G (**13*), c.1905+1G>A (**2A*), and c.2846A>T [11]. The combined carrier frequency of these four alleles in European and North American populations is approximately 2%–8% [12, 13].

Although there has been extensive investigation into the risk of moderate-to-severe fluoropyrimidine toxicity in patients with pathogenic *DPYD* variants, reliable estimates for the risk of treatment-related death in these patients are lacking, primarily because of the rarity of grade 5 events in unselected patients. We conducted a systematic review and meta-analysis to better estimate the risk of treatment-related death in carriers of pathogenic *DPYD* gene variants who receive standard-dose fluoropyrimidine chemotherapy.

Materials and Methods

Systematic Review

We conducted a systematic literature review, with adherence to the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement [14]. The study protocol was reviewed by the Committee for the Protection of Human Subjects at Dartmouth College, with a determination that the research did not meet the regulatory definition of human subject research. This review is registered in the PROSPERO prospective register of systematic reviews (ID CRD42020144921) [15, 16].

We initially searched the MEDLINE (PubMed), Embase (OVID), Web of Science, and Cochrane Library (Wiley) databases to identify relevant articles published prior to January 24, 2018; the search was limited to English language reports (papers and abstracts). We subsequently updated and repeated our search to include reports published through September 17, 2020. The final search strategy employed a combination of Medical Subject Heading terms and keyword terms. The search strategy was adjusted for the syntax appropriate to each database. A description of the terms used in the MEDLINE search is included in Table 1; similar terms were used in the Embase, Web of Science, and Cochrane Library searches.

Table 1. MEDLINE search strategy

Search	Query	Results
#1	Search: "Dihydropyrimidine Dehydrogenase Deficiency"[MeSH] OR "Dihydrouracil Dehydrogenase (NADP)"[MeSH] OR Dihydrouracil dehydrogenase[tiab] OR Dihydropyrimidine dehydrogenase [tiab] OR DPYD*[tiab] OR DPD[tiab] OR 1905+1G>A[tiab] OR c.1905+1G>A [tiab] OR IVS14+1G>A[tiab] OR rs3918290[tiab] OR 2846A>T[tiab] OR c.2846A>T[tiab] OR D949V[tiab] OR p.D949V[tiab] OR Asp949Val[tiab] OR p.Asp949Val[tiab] OR rs67376798[tiab] OR 1679T>G[tiab] OR c.1679T>G[tiab] OR I560S[tiab] OR p.I560S[tiab] OR Ile560Ser[tiab] OR p.Ile560Ser[tiab] OR rs55886062[tiab] OR HapB3[tiab] OR 1129-5923C>G[tiab] OR c.1129-5923C>G[tiab] OR 1236G>A[tiab] OR c.1236G>A[tiab] OR E412E[tiab] OR p.E412E[tiab] OR Glu412Glu[tiab] OR p.Glu412Glu[tiab] OR rs56038477[tiab] OR rs75017182[tiab]	4,222
#2	Search: "Fluorouracil"[MeSH] OR "Capecitabine"[MeSH] OR 5Fluorouracil[tiab] OR 5-Fluorouracil [tiab] OR Fluorouracil[tiab] OR 5FU [tiab] OR 5-FU[tiab] OR Capecitabine [tiab] OR Fluoropyrimidine*[tiab]	64,546
#3	Search: "Humans"[MeSH] OR patient* [tiab] OR human*[tiab]	20,251,398
#4	Search: #1 AND #2 AND #3	1,550

We limited our review to research publications and abstracts describing studies of adult patients with solid tumor (nonhematologic) malignancies treated with standard doses of fluoropyrimidine chemotherapy (5-fluorouracil or capecitabine). We further limited our review to studies in which patients were systematically tested for one or more of the four pathogenic *DPYD* variants of interest (c.1129-5923C>G, c.1679T>G, c.1905+1G>A, and/or c.2846A>T) with prospective biospecimen collection and followed after chemotherapy initiation for assessment of treatment-related adverse events. We excluded case-control studies and other studies that selectively tested patients for *DPYD* gene variants based on toxicities or decreased DPD activity, as well as studies that did not identify carriers of any of the four variants of interest.

We conducted the manual review of studies in two phases. In the initial phase we screened study titles and abstracts to identify potentially eligible studies, using the Rayyan software app to organize the review process (Cambridge, Massachusetts, U.S.A.) [17]. In the second phase we reviewed the full text of

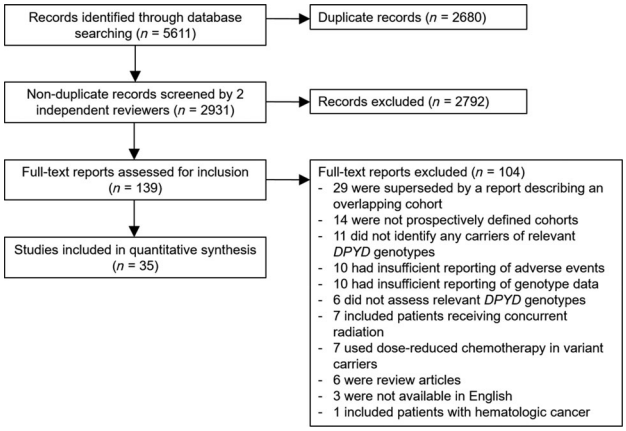

Figure 1. PRISMA diagram of included studies.

published manuscripts and abstracts to determine study inclusion and exclusion, referencing published appendix materials as necessary. In cases in which overlapping cohorts were described in multiple reports, we abstracted a single record for the cohort using relevant data from any of the published reports. Each stage of the review process was carried out in duplicate by two independent reviewers, and conflicting decisions were resolved through discussion among authors B.B.S., K.R., and G.A.B.

Data Extraction

Two reviewers extracted relevant data from published manuscripts, appendix materials, and abstracts of included studies. Data items collected included study design, study location, characteristics of the patient population, fluoropyrimidine agent (5-fluoroacil [5-FU], capecitabine, or either), chemotherapy regimen type (fluoropyrimidine monotherapy or combination chemotherapy), treatment setting (adjuvant, metastatic, or unspecified), *DPYD* variants evaluated, the number of patients evaluated for each *DPYD* variant, the number of patients with identified *DPYD* variants, the number of patients with treatment-related mortality (i.e., grade 5 toxicity), and any available information about the *DPYD* genotype of decedents. We accepted author reporting of treatment-related deaths, as opposed to cancer-related mortality, based on study-specific definitions or reporting. We contacted study authors by e-mail with requests for clarification when information regarding the number of variant carriers, the number of decedents, or the genotype of decedents was unclear. Data were collected and managed using study-specific REDCap electronic data capture tools (Vanderbilt University, Nashville, TN) hosted at the Dartmouth-Hitchcock Medical Center [18, 19].

Risk-of-Bias Evaluation

We used the CLARITY Tool to assess risk of bias in cohort studies to guide our risk-of-bias evaluation [20]. The study design controlled for items 1–5, 7, and 8 in the CLARITY Tool. We evaluated the risk of bias in our analysis by answering question 6 of the tool, which reads "Can we be confident in the assessment of [the] outcome?" (Categorized as "yes," "probably yes," "probably no," or "no"). Studies were classified as "yes" if explicit mention was made that treatment-related deaths (or grade 5 toxicities) did or did not occur. Studies were classified as "probably yes" if there was detailed reporting of adverse events and grading of events, without explicit mention that treatment-related deaths did or did not occur. Studies that reported only summary information about adverse events were classified as "probably no." When assessing for risk of bias in reporting of treatment-related mortality, we used all available information collected for each study, including author query e-mail responses, when available.

Data Synthesis

The primary study outcome was the relative risk of treatment-related mortality in patients who were carriers of pathogenic *DPYD* variants, compared with noncarriers. Treatment-related mortality is a rare event (with no observed events from one or both cohorts of many of the included studies), and meta-analysis of rare events poses special methodological challenges [21, 22]. We pooled the study-level data using a Mantel-Haenszel fixed effects model. An advantage of this approach is that it does not employ an arbitrary continuity correction for studies with no events in one of two compared groups [21]; however, studies with no events in either of the two compared groups are excluded from the pooled analysis of relative risk with this approach. Study heterogeneity was assessed using the I^2 index [23].

We performed two sensitivity analyses for the comparison of patients with and without identified *DPYD* variants. The first sensitivity analysis excluded studies with high risk of bias, in which confidence in the outcome assessment was lacking. The second sensitivity analysis excluded studies of fewer than 200 patients, in which publication bias could lead to selective publication of studies with higher incidence of treatment-related adverse events.

We also estimated the absolute risk of treatment-related mortality for subgroups of patients defined by their carrier status for specific *DPYD* variants. Subgroups included patients with of any of the four *DPYD* variants evaluated, each of the four studied *DPYD* variants individually, and for the group of patients with any one of the three variants including c.1679T>G, c.1905+1G>A, and/or c.2846A>T (excluding patients with only the c.1129-5923C>G genotype, which may confer lesser risk for severe toxicity than the other three variants [24]). We used Mantel-Haenszel fixed effects models to construct pooled estimates of absolute mortality risk across the included studies (including studies with no treatment-related deaths.)

Statistical analyses were implemented in R (R Foundation, Vienna), using package "meta" [25, 26]. Lastly, we composed a narrative synthesis to describe treatment-related mortality among patients with homozygosity or compound heterozygosity for pathogenic *DPYD* variants.

Results

Search Results

Our database search identified 2,928 unique study records. After dual review of manuscripts and abstracts captured in the initial search, we identified 35 studies for inclusion in our analysis [10, 13, 27–59]. Details of the review process are shown in Figure 1. Ten of 35 included studies were prospective clinical trials, 16 were prospective cohort studies,

Table 2. Summary characteristics of 35 included studies and 13,929 included patients

Characteristics	Studies, *n* (%)	Patients tested for ≥1 *DPYD* variant, *n* (%)
Study design		
Clinical trial	10 (28.6)	8,422 (60.5)
Observational study, prospective	16 (45.7)	2,813 (20.2)
Observational study, retrospective	9 (25.7)	2,694 (19.3)
Number of patients in cohort		
<200	16 (45.7)	1,404 (10.1)
≥200	19 (54.3)	12,525 (89.9)
Study continent		
Europe	26 (74.3)	9,925 (71.3)
Asia	6 (17.1)	525 (3.8)
North America	3 (8.6)	3,479 (25.0)
Cancer site		
Colorectal	20 (57.1)	9,603 (68.9)
Gastrointestinal (noncolorectal)	2 (5.7)	127 (0.9)
Breast	2 (5.7)	348 (2.5)
Multiple sites included	11 (31.4)	3,851 (27.6)
Treatment setting		
Adjuvant	5 (14.3)	5,625 (40.4)
Metastatic	11 (31.4)	2,877 (20.7)
Mixed or not described	19 (54.3)	5,427 (39.0)
Fluoropyrimidine agent		
5-FU	15 (42.9)	8,405 (60.3)
Capecitabine	7 (20.0)	2,083 (15.0)
5-FU or capecitabine	13 (37.1)	3,441 (24.7)
Chemotherapy regimen type		
Monotherapy only	4 (11.4)	1,782 (12.8)
Combination therapy[a]	31 (88.6)	12,147 (87.2)
DPYD gene variants assessed		
c.1129-5923C>G	11 (31.4)	6,242 (44.8)
c.1679T>G	17 (48.6)	8,799 (63.2)
c.1905+1G>A	35 (100)	13,929 (100)
c.2846A>T	23 (65.7)	10,759 (77.2)

[a]Multi-arm studies were classified as combination therapy if any of the study arms involved combination chemotherapy.
Abbreviation: 5-FU, 5-fluorouracil.

and 9 were retrospective studies of cohorts with prospective biospecimen collection. Aggregate characteristics of included studies are shown in Table 2 and individual studies are described in Table 3.

Risk-of-Bias Assessment

We identified incomplete outcome assessment (incomplete assessment and reporting of treatment-related death) as the primary risk of bias affecting our analysis. After incorporating information from responses to author queries, we assessed 19 included studies (54%) as having low risk of bias in outcome reporting, 12 studies (34%) as having moderate risk of bias, and 4 studies (11%) as having high risk of bias. Studies at very high risk of bias (very low confidence in outcome assessment) were excluded by the study design.

DPYD Variants and Association with Treatment-Related Mortality

The study evaluated 13,929 patients for one or more *DPYD* variant (including c.1129-5923C>G, c.1679T>G, c.1905+1G>A, and/or c.2846A>T) across the 35 included studies. Pathogenic *DPYD* variants were identified in 566 patients (4.1%). The pooled carrier frequency for each of the four studied *DPYD* variants is shown in Table 4. The c.1129-5923C>G genotype was the most common abnormality, occurring in 3.9% of 6,242 patients evaluated for this variant. Study-level information about patients tested for individual *DPYD* variants is shown in the supplemental online Table 1.

Twenty-seven treatment-related deaths were reported among 13,929 patients receiving standard doses of fluoropyrimidine-based chemotherapy, for a crude treatment-related mortality rate of 0.2%. At least one treatment-related death was reported in 13 of the 35 studies. There were 14 treatment-related deaths in 13,364 patients without identified *DPYD* variants (mortality = 0.1%; 95% CI, 0.1–0.2) and 13 treatment-related deaths in 566 patients with identified *DPYD* variants (mortality = 2.3%; 95% CI, 1.3%–3.9%). Estimates of risk for treatment-related mortality associated with specific *DPYD* gene variants are shown in Table 4.

The 13 studies with at least one treatment-related death contributed to the meta-analytic estimate of relative risk. Patients who were carriers of a pathogenic *DPYD* gene variant had a 25.6 times increased risk of treatment-related mortality (95% CI, 12.1–53.9; $I^2 = 8.2\%$). The forest plot summarizing the results of individual studies contributing to the pooled estimate results is shown in Figure 2. The findings of the main analysis are supported by two prespecified sensitivity analyses; one limited to the 31 studies with low to moderate risk of bias in outcome assessment (risk ratio [RR] = 21.6; 95% CI, 9.8–47.5) and the second limited to 19 studies of ≥200 patients (RR = 29.3; 95% CI, 12.2–70.2).

Homozygosity and Compound Heterozygosity

Among the 566 patients carrying pathogenic *DPYD* variants, seven patients had identified homozygosity or compound heterozygosity of pathogenic *DPYD* variants. Three patients were reported to be homozygous for c.1905+1G>A; no deaths were reported in these patients, although all had grade 4 toxicity [29, 41]. Two patients were reported to be homozygous for c.1129-5923 C>G, with one experiencing treatment-related death [13, 42]. Two patients had compound heterozygosity, including one patient who was a carrier of c.1905+1G>A and c.2846A>T and another patient who was a carrier of c.1679G>A and c.1905+1G>A; both patients had treatment-related death [13, 46].

Discussion

The most commonly reported safety outcome in studies of chemotherapy treatment is the incidence of grade 3 or

Table 3. Descriptive characteristics of 35 studies included in the systematic review

Study	Study design	*DPYD* genotypes evaluated	*DPYD* variant carriers, *n* / Patients evaluated, *n*[a]	Deaths in variant carriers, *n* / All deaths, *n*	Confident in outcome assessment [20]?
Salgueiro, 2004 [27]	PC	c.1905+1G>A	1/73	0	Yes
Largillier, 2006 [28]	PC	c.1905+1G>A	1/105	1/1	Probably yes
Morel, 2006 [29]	PC	c.1679T>G, c.1905+1G>A, c.2846A>T	21/487	1/1	Yes
Salgado, 2007 [30]	PC	c.1905+1G>A	1/58	0	Yes
Schwab, 2008 [31]	CT	c.1905+1G>A	13/683	0	Yes
Gross, 2008 [32]	RC	c.1129-5923C>G, c.1905 +1G>A, c.2846A>T	7/128	0/2	Yes
Braun, 2009 (FOCUS) [33]	CT	c.1905+1G>A	4/629	0	Probably no[b]
Boige, 2010 (FFCD 2000-005) [34]	CT	c.1905+1G>A	2/346	0	Probably yes[b]
Ceric, 2010 [35]	PC	c.1905+1G>A	1/50	1/2	Yes
Kristensen, 2010 [36]	RC	1679T>G, c.1905+1G>A, c.2846A>T	3/68	0	Yes
Deenen, 2011 (CAIRO2) [37]	CT	c.1129-5923C>G, 1679T>G, c.1905+1G>A, c.2846A>	44/568	1/1	Probably yes
Dhawan, 2013 [38]	PC	c.1905+1G>A, c.2846A>T	9/23	0	Probably no
Loganayagam, 2013 [39]	RC	c.1129-5923C>G, 1679T>G, c.1905+1G>A, c.2846A>T	25/430	0	Yes
Jennings, 2013 [40]	PC	c.1129-5923C>G, c.1905 +1G>A, c.2846A>T	15/254	1/4	Yes
Rosmarin, 2014 (QUASAR2) [10]	CT	c.1905+1G>A, c.2846A>T[c]	54/909	2/2	Yes
Cai, 2014 [41]	PC	c.1905+1G>A	13/80	0	Probably no
Froehlich, 2015 [42]	PC	c.1129-5923C>G, 1679T>G, c.1905+1G>A, c.2846A>T	32/500	1/1	Probably yes
Lee, 2014 (NCCTG N0147) [13, 24]	CT	c.1129-5923C>G, 1679T>G, c.1905+1G>A, c.2846A>T	133/2,594	1/1	Probably yes
Etienne-Grimaldi, 2014 [43]	CT	c.1905+1G>A	3/205	0	Yes[b]
Joerger, 2015 [44]	PC	c.1905+1G>A, c.2846A>T	8/140	0	Yes[b]
Falvella, 2015 [45]	PC	c.1129-5923C>G, 1679T>G, c.1905+1G>A, c.2846A>T	3/64	0	Probably yes
Toffoli, 2015 [46]	RC	1679T>G, c.1905+1G>A, c.2846A>T	18/603	1/1	Probably yes
Ohnuma, 2015 [47]	RC	c.1905+1G>A	1/103	0	Probably yes
Boige, 2016 (PETACC-8) [48]	CT	c.1129-5923C>G, 1679T>G, c.1905+1G>A, c.2846A>T	89/1,545	0	Yes[b]
Botticelli, 2017 [49]	RC	c.1905+1G>A,	6/638	0	Yes[b]
Boisdron-Celle, 2017 [50]	PC	c.1679T>G, c.1905+1G>A, c.2846A>T	11/398	1/1	Yes
Etienne-Grimaldi, 2017 [51]	PC	c.1129-5923C>G, 1679T>G, c.1905+1G>A, c.2846A>T	11/243	1/1	Yes
Ruzzo, 2017 (TOSCA) [52]	CT	c.1679T>G, c.1905+1G>A, c.2846A>T	9/508	0	Yes[b]
Vivaldi, 2017 [53]	PC	c.1679T>G, c.1905+1G>A, c.2846A>T	1/104	0	Yes[b]
Nahid, 2018 [54]	PC	c.1905+1G>A	8/161	0	Probably yes
Cremolini, 2018 (TRIBE) [55]	CT	c.1679T>G, c.1905+1G>A, c.2846A>T	10/439	1/9	Yes[b]
Amirfallah, 2018 [56]	RC	c.1679T>G, c.1905+1G>A, c.2846A>T	1/85	0	Probably no
Toffoli, 2019 [57]	RC	c.1129-5923C>G, 1679T>G, c.1905+1G>A, c.2846A>T	37/550	0	Yes

(continued)

Table 3. (continued)

Study	Study design	*DPYD* genotypes evaluated	*DPYD* variant carriers, *n* / Patients evaluated, *n*[a]	Deaths in variant carriers, *n* / All deaths, *n*	Confident in outcome assessment [20]?
Alvarado Fernández, 2019 [58]	RC	c.1129-5923C>G, 1679T>G, c.1905+1G>A, c.2846A>T	3/89	0	Probably yes
Negarandeh, 2020 [59]	PC	c.1905+1G>A, c.2846A>T	4/73	0	Probably yes

[a]Numerator indicates number of patients carrying one or more *DPYD* variants. Denominator indicates the number of patients in the cohort who were tested for one or more *DPYD* variants.
[b]Response from author query contributed to the assessment of confidence in outcome assessment.
[c]Data from this study for carriers of c.1129-5923C>G was excluded because of methodologic concerns. Carrier status for c.1129-5923C>G was imputed using rs281121; this reference single nucleotide polymorphism is located on chromosome 5, whereas the *DPYD* gene localizes to chromosome 1.
Abbreviations: CT, clinical trial; PC, prospective cohort, RC, retrospective cohort.

Table 4. Risk of death by *DPYD* genotype in patients undergoing standard-dose fluoropyrimidine chemotherapy

DPYD variants	Patients tested, *n*	Variant carriers, *n* (%)	Deaths in variant carriers, *n*[a]	Risk of death in variant carriers, % (95% CI)
c.1129-5923C>G	6,242	241 (3.9)	1	0.4 (0.1–2.9)
c.1679T>G	8,799	17 (0.2)	1	5.9 (0.8–32.0)
c.1905+1G>A	13,929	183 (1.3)	8	4.4 (2.2–8.5)
c.2846A>T	10,759	127 (1.2)	5	3.9 (1.7–9.1)
Any of four variants (c.1236G>A, c.1679T>G, c.1905+1G>A, or c.2846A>T)	13,929[b]	566 (4.1)	13	2.3 (1.3–3.9)
Any of three variants (c.1679T>G, c.1905+1G>A, or c.2846A>T)	13,929[b]	325 (2.3)	12	3.7 (2.1–6.4)

[a]Two deaths occurred in patients with compound heterozygosity of *DPYD* gene variants.
[b]Includes patients with evaluation for one or more of the four studied variants.
Abbreviations: CI, confidence interval.

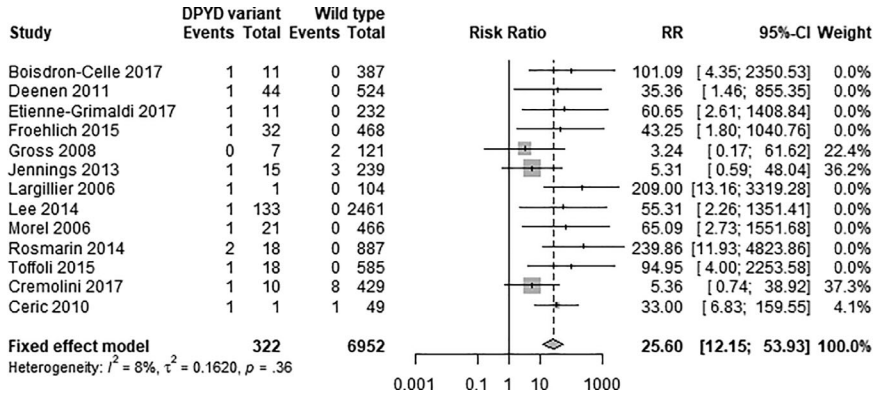

Figure 2. Forest plot for the association of *DPYD* variants with treatment-related death.
Abbreviations: CI, confidence interval; RR, risk ratio.

higher adverse events, as codified by the Common Terminology Criteria for Adverse Events (CTCAE) [60]. Treatment-attributable deaths are coded as grade 5 toxicities on the CTCAE scale; however, these events are rare enough in most studies (typically occurring in fewer than 1% of patients) that grade 5 toxicities are rarely reported as a key safety outcome. Still, there can be little debate that treatment-related deaths are the most consequential toxicity events in cancer treatment.

In this systematic review and pooled analysis, we describe the risk of treatment-related mortality in patients with and without uncommon pathogenic variants of the *DPYD* gene who received fluoropyrimidine-containing chemotherapy (5-FU or capecitabine). Across the 35 included studies we identified 27 deaths in 13,929 patients, for a crude risk of treatment-related death risk of 0.2%. This observed risk is similar to mortality figures reported in other large cohorts; the IDEA collaborators reported 19 treatment-related deaths among

12,834 patients receiving adjuvant FOLFOX or CAPOX (mortality risk = 0.15%) [3], and Cheung et al. report a 60-day mortality risk of 0.6% among 37,568 patients with colon cancer participating in clinical trials of adjuvant therapy between 1977 and 2016 [5].

Although treatment-related mortality was generally low across the studies included in our analysis, patients with uncommon *DPYD* variants had an estimated 25.6 times increased risk for treatment-related death. The absolute risk of death among patients carrying any of the four evaluated *DPYD* variants was 2.3%. Risk of death was still higher after excluding the more common but less deleterious c.1129-5923 C>G variant; patients carrying the c.1905+1G>A, c.1679T>G, or c.2846A>T variants had a mortality risk of 3.7%. These findings suggest that the number needed to test to prevent one treatment-related death with *DPYD* genotyping is approximately 1,000–1,200 patients, (with a number needed to treat to prevent grade ≥3 toxicity that is considerably lower).

Our findings describe the largest analysis to date of treatment-related mortality in *DPYD* variant carriers. Deenen et al. have previously estimated a treatment-related mortality of roughly 10% in patients carrying the *DPYD* c.1905+1G>A variant, based on their systematic review of 3,974 patients (with 5 deaths among 48 patients carrying the c.1905+1G>A variant) [7]. It is particularly notable in our analysis that *DPYD* variants were identified in roughly half of all patients who experienced treatment-related mortality. It is possible that still more of the decedents carried unidentified *DPYD* abnormalities, as genotype information was incomplete for one or more of the four variants of interest in each of the decedents without an identified variant of the *DPYD* gene.

Our analysis adds to a strong and growing evidence base demonstrating that *DPYD* variants lead to increased risk of severe and sometimes fatal toxicity during treatment with standard-dose fluoropyrimidine chemotherapy. This evidence base includes at least three prospective studies linking pharmacogenetic testing and proactive chemotherapy dose reduction with lower risk for severe toxicities and deaths [7, 12, 50]. Recommendations for genotype-guided fluoropyrimidine dose reductions have been formalized in an iteratively-revised guideline from the Clinical Pharmacogenetics Implementation Consortium [61], and there are growing calls to implement universal *DPYD* variant testing (or other screening for DPD deficiency) prior to fluoropyrimidine chemotherapy [62, 63]. In April of 2020 the European Medicines Agency took the regulatory stance of recommending universal DPD deficiency screening for European patients prior to fluoropyrimidine chemotherapy [64], and screening for DPD deficiency has become standard practice in many areas of Europe and the U.K.

Screening for pathogenic *DPYD* gene variants or DPD deficiency is not formally recommended by U.S. authorities at this time. Nevertheless, the U.S. Food and Drug Administration (FDA) has taken multiple actions in recent years in recognition of the risk of severe toxicity from fluoropyrimidine chemotherapy. In December of 2015 the FDA approved uridine triacetate as an antidote to overdose or early-onset severe toxicity from 5-fluorouracil or capecitabine, when given within 96 hours of last drug exposure. Approval was based on two studies of 135 patients combined, and 87% of these patients had fluoropyrimidine overdose rather than early-onset toxicity [65]. The efficacy of uridine triacetate for preventing severe, delayed onset fluoropyrimidine toxicity in carriers of pathogenic *DPYD* gene variants is unknown, as severe symptoms in carriers of *DPYD* gene variants often present greater than 96 hours after drug exposure. Additionally, in February of 2020 the FDA published its Table of Pharmacogenetic Associations, therein recognizing that pathogenic *DPYD* gene variants are associated with increased risk of "severe, life-threatening or fatal toxicities" from fluorouracil or capecitabine and that data support therapeutic management recommendations for carriers of these variants [66].

A key strength of this study is the systematic approach to identify rare events in unselected patients with and without uncommon genetic variants. Our findings must be interpreted in the context of certain limitations. Although our search strategy excluded studies with the highest risk for bias, we could not eliminate all sources of bias. Only 9 of the 35 included studies assessed each of the four *DPYD* variants of interest, and it is likely that some decedents without identified *DPYD* variants may have been misclassified. Because treatment-related mortality is a rare event, it was not defined or reported as a primary safety outcome for most of the included studies. There is some residual risk that investigators of included studies may have been more likely to report deaths in *DPYD* variant carriers as treatment-related (selective outcome reporting bias). Additionally, it is possible that some treatment-related deaths may have been misattributed to disease progression (false negatives). We had low confidence in outcome reporting for 6 of the 35 included studies; however, results of a sensitivity analysis excluding these studies did not differ meaningfully from the findings of the main analysis. The generalizability of our findings is also influenced by the included patient population. Most included studies were based in Europe, where these four pathogenic *DPYD* variants have been best studied.

Conclusion

We found that patients receiving standard doses of fluoropyrimidine chemotherapy who were carriers of pathogenic *DPYD* gene variants had a 25.6 times increased risk of treatment-related mortality, with an absolute mortality risk of up to 3.7% for patients carrying any of the c.1905+1G>A, c.1679T>G, or c.2846A>T variants. This information is useful for appraising the clinical utility of *DPYD* genotyping for preventing severe toxicity and death in patients planned to receive standard-dose fluoropyrimidine chemotherapy. Together with data from prospective trials showing that fluoropyrimidine dose reductions are protective against severe chemotherapy toxicities in *DPYD* variant carriers [7, 12, 50], our findings give additional support for the use of *DPYD* genotyping as an effective tool for identifying patients at risk for fatal toxicity from fluoropyrimidine chemotherapy.

Acknowledgments

This research was supported by The Dartmouth-Hitchcock Cancer Research Fellows Program (to G.A.B.), the Cancer

Clinical Investigator Team Leadership Award (CCITLA) awarded by the National Cancer Institute (NCI) Coordinating Center for Clinical Trials (to G.A.B.), The Dartmouth Clinical and Translational Science Institute, (under award number UL1TR001086 from the National Center for Advancing Translational Sciences [NCATS] of the National Institutes of Health [NIH]), and the Biostatistics Shared Resource of the Norris Cotton Cancer Center (NCCC) at Dartmouth. The CCITLA and the Biostatistics Shared Resource are funded by NCCC's NCI Cancer Center Support Grant 5P30CA023108-40). The content of this manuscript is solely the responsibility of the authors and does not necessarily represent the official views of the NIH, NCI, or NCATS.

Author Contributions

Conception/design: Bhavina B. Sharma, Karan Rai, Heather Blunt, Tor D. Tosteson, Gabriel A. Brooks
Provision of study material or patients: Gabriel A. Brooks
Collection and/or assembly of data: Bhavina B. Sharma, Karan Rai, Gabriel A. Brooks
Data analysis and interpretation: Bhavina B. Sharma, Karan Rai, Heather Blunt, Wenyan Zhao, Tor D. Tosteson, Gabriel A. Brooks
Manuscript writing: Bhavina B. Sharma, Karan Rai, Gabriel A. Brooks
Final approval of manuscript: Bhavina B. Sharma, Karan Rai, Heather Blunt, Wenyan Zhao, Tor D. Tosteson, Gabriel A. Brooks

Disclosures

The authors indicated no financial relationships.

References

1. Levy E, Piedbois P, Buyse M et al. Toxicity of fluorouracil in patients with advanced colorectal cancer: Effect of administration schedule and prognostic factors. J Clin Oncol 1998;16:3537–3541.

2. Twelves C, Wong A, Nowacki MP et al. Capecitabine as adjuvant treatment for stage III colon cancer. N Engl J Med 2005;352:2696–2704.

3. Grothey A, Sobrero AF, Shields AF et al. Duration of adjuvant chemotherapy for stage III colon cancer. N Engl J Med 2018;378:1177–1188.

4. Andre T, Boni C, Mounedji-Boudiaf L et al. Oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment for colon cancer. N Engl J Med 2004;350:2343–2351.

5. Cheung WY, Renfro LA, Kerr D et al. Determinants of early mortality among 37,568 patients with colon cancer who participated in 25 clinical trials from the adjuvant colon cancer endpoints database. J Clin Oncol 2016;34:1182–1189.

6. van Kuilenburg AB. Dihydropyrimidine dehydrogenase and the efficacy and toxicity of 5-fluorouracil. Eur J Cancer 2004;40:939–950.

7. Deenen MJ, Meulendijks D, Cats A et al. Upfront genotyping of DPYD*2A to individualize fluoropyrimidine therapy: A safety and cost analysis. J Clin Oncol 2016;34:227–234.

8. Ezzeldin H, Diasio R. Dihydropyrimidine dehydrogenase deficiency, a pharmacogenetic syndrome associated with potentially life-threatening toxicity following 5-fluorouracil administration. Clin Colorectal Cancer 2004;4:181–189.

9. Terrazzino S, Cargnin S, Del Re M et al. A DPYD IVS14+1G>A and 2846A>T genotyping for the prediction of severe fluoropyrimidine-related toxicity: a meta-analysis. Pharmacogenomics 2013;14:1255–1272.

10. Rosmarin D, Palles C, Church D et al. Genetic markers of toxicity from capecitabine and other fluorouracil-based regimens: Investigation in the QUASAR2 study, systematic review, and meta-analysis. J Clin Oncol 2014;32:1031–1039.

11. Innocenti F, Mills SC, Sanoff H et al. All you need to know about DPYD genetic testing for patients treated with fluorouracil and capecitabine: A practitioner-friendly guide. JCO Oncol Pract 2020;16:793–798.

12. Henricks LM, Lunenburg C, de Man FM et al. DPYD genotype-guided dose individualisation of fluoropyrimidine therapy in patients with cancer: A prospective safety analysis. Lancet Oncol 2018;19:1459–1467.

13. Lee AM, Shi Q, Pavey E et al. DPYD variants as predictors of 5-fluorouracil toxicity in adjuvant colon cancer treatment (NCCTG N0147). J Natl Cancer Inst 2014;106:dju298.

14. Moher D, Liberati A, Tetzlaff J et al. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. PLoS Med 2009;6:e1000097.

15. Booth A, Clarke M, Ghersi D et al. An international registry of systematic-review protocols. Lancet 2011;377:108–109.

16. PROSPERO. International prospective register of systematic reviews. National Institute for Health Research Web site. Available at https://www.crd.york.ac.uk/prospero/. Accessed November 22, 2019.

17. Ouzzani M, Hammady H, Fedorowicz Z et al. Rayyan-A web and mobile app for systematic reviews. Syst Rev 2016;5:210.

18. Harris PA, Taylor R, Minor BL et al. The REDCap consortium: Building an international community of software platform partners. J Biomed Inform 2019;95:103208.

19. Harris PA, Taylor R, Thielke R et al. Research electronic data capture (REDCap)–a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform 2009;42:377–381.

20. CLARITY Group at McMaster University. Tool to assess risk of bias in cohort studies. Available at https://www.evidencepartners.com/wp-content/uploads/2017/09/Tool-to-Assess-Risk-of-Bias-in-Cohort-Studies.pdf. Accessed November 26, 2019.

21. Efthimiou O. Practical guide to the meta-analysis of rare events. Evid Based Ment Health 2018;21:72–76.

22. Bhaumik DK, Amatya A, Normand SL et al. Meta-analysis of rare binary adverse event data. J Am Stat Assoc 2012;107:555–567.

23. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med 2002;21:1539–1558.

24. Lee AM, Shi Q, Alberts SR et al. Lee AM, Shi Q, Alberts SR et al. Association between DPYD c.1129-5923 C>G/hapB3 and severe toxicity to 5-fluorouracil-based chemotherapy in stage III colon cancer patients. Pharmacogenetics and Genomics 2016;26:133–137.

25. R Core Team. A language and environment for statistical computing. R Foundation for Statistical Computing Web site, 2021. Available at https://www.R-project.org/. Accessed March 12, 2021.

26. Balduzzi S, Rücker G, Schwarzer G. How to perform a meta-analysis with R: A practical tutorial. Evid Based Ment Health 2019;22:153–160.

27. Salgueiro N, Veiga I, Fragoso M et al. Mutations in exon 14 of dihydropyrimidine dehydrogenase and 5-fluorouracil toxicity in Portuguese colorectal cancer patients. Genet Med 2004;6:102–107.

28. Largillier R, Etienne-Grimaldi MC, Formento JL et al. Pharmacogenetics of capecitabine in advanced breast cancer patients. Clin Cancer Res 2006;12:5496–5502.

29. Morel A, Boisdron-Celle M, Fey L et al. Clinical relevance of different dihydropyrimidine dehydrogenase gene single nucleotide polymorphisms on 5-fluorouracil tolerance. Mol Cancer Ther 2006;5:2895–2904.

30. Salgado J, Zabalegui N, Gil C et al. Polymorphisms in the thymidylate synthase and dihydropyrimidine dehydrogenase genes predict response and toxicity to capecitabine-raltitrexed in colorectal cancer. Oncol Rep 2007;17:325–328.

31. Schwab M, Zanger UM, Marx C et al. Role of genetic and nongenetic factors for fluorouracil treatment-related severe toxicity: A prospective clinical trial by the German 5-FU Toxicity Study Group. J Clin Oncol 2008;26:2131–2138.

32. Gross E, Busse B, Riemenschneider M et al. Strong association of a common dihydropyrimidine dehydrogenase gene polymorphism with fluoropyrimidine-related toxicity in cancer patients. PloS One 2008;3:e4003.

33. Braun MS, Richman SD, Thompson L et al. Association of molecular markers with toxicity outcomes in a randomized trial of chemotherapy for advanced colorectal cancer: The FOCUS trial. J Clin Oncol 2009;27:5519–5528.

34. Boige V, Mendiboure J, Pignon JP et al. Pharmacogenetic assessment of toxicity and outcome in patients with metastatic colorectal cancer treated with LV5FU2, FOLFOX, and FOLFIRI: FFCD 2000-05. J Clin Oncol 2010;28:2556–2564.

35. Ceric T, Obralic N, Kapur-Pojskic L et al. Investigation of IVS14 + 1G > A polymorphism of DPYD gene in a group of Bosnian patients treated with 5-Fluorouracil and capecitabine. Bosn J Basic Med Sci 2010;10:133–139.

36. Kristensen MH, Pedersen PL, Melsen GV et al. Variants in the dihydropyrimidine dehydrogenase, methylenetetrahydrofolate reductase and thymidylate synthase genes predict early toxicity of 5-fluorouracil in colorectal cancer patients. J Int Med Res 2010;38:870–883.

37. Deenen MJ, Tol J, Burylo AM et al. Relationship between single nucleotide polymorphisms and haplotypes in DPYD and toxicity and efficacy of capecitabine in advanced colorectal cancer. Clin Cancer Res 2011;17:3455–3468.

38. Dhawan D, Panchal H, Shukla S et al. Genetic variability & chemotoxicity of 5-fluorouracil & cisplatin in head & neck cancer patients: A preliminary study. Indian J Med Res 2013;137: 125–129.

39. Loganayagam A, Arenas Hernandez M, Corrigan A et al. Pharmacogenetic variants in the DPYD, TYMS, CDA and MTHFR genes are clinically significant predictors of fluoropyrimidine toxicity. Br J Cancer 2013;108:2505–2515.

40. Jennings BA, Loke YK, Skinner J et al. Evaluating predictive pharmacogenetic signatures of adverse events in colorectal cancer patients treated with fluoropyrimidines. PLoS One 2013;8:e78053.

41. Cai X, Fang JM, Xue P et al. The role of IVS14+1 G > A genotype detection in the dihydropyrimidine dehydrogenase gene and pharmacokinetic monitoring of 5-fluorouracil in the individualized adjustment of 5-fluorouracil for patients with local advanced and metastatic colorectal cancer: A preliminary report. Eur Rev Med Pharmacol Sci 2014;18:1247–1258.

42. Froehlich TK, Amstutz U, Aebi S et al. Clinical importance of risk variants in the dihydropyrimidine dehydrogenase gene for the prediction of early-onset fluoropyrimidine toxicity. Int J Cancer 2015;136:730–739.

43. Etienne-Grimaldi MC, Hebbar M, Gramont AD et al. Multivariate prospective pharmacogenetic analysis in patients with resectable metastatic colorectal cancer (mCRC) receiving FOLFOX chemotherapy. J Clin Oncol 2014;32(suppl 15): 3569a.

44. Joerger M, Huitema AD, Boot H et al. Germline TYMS genotype is highly predictive in patients with metastatic gastrointestinal malignancies receiving capecitabine-based chemotherapy. Cancer Chemother Pharmacol 2015;75:763–772.

45. Falvella FS, Cheli S, Martinetti A et al. DPD and UGT1A1 deficiency in colorectal cancer patients receiving triplet chemotherapy with fluoropyrimidines, oxaliplatin and irinotecan. Br J Clin Pharmacol 2015;80:581–588.

46. Toffoli G, Giodini L, Buonadonna A et al. Clinical validity of a DPYD-based pharmacogenetic test to predict severe toxicity to fluoropyrimidines. Int J Cancer 2015;137:2971–2980.

47. Ohnuma S, Toshima M, Miura K et al. Single-nucleotide polymorphisms of DPYD predict adverse events associated with 5-fluorouracil in patients with gastrointestinal cancer. Ann Oncol 2015;26(suppl 9):ix11.

48. Boige V, Vincent M, Alexandre P et al. DPYD genotyping to predict adverse events following treatment with fluorouracil-based adjuvant chemotherapy in patients with stage III colon cancer: A secondary analysis of the PETACC-8 randomized clinical trial. JAMA Oncol 2016;2:655–662.

49. Botticelli A, Onesti CE, Strigari L et al. A nomogram to predict 5-fluorouracil toxicity: When pharmacogenomics meets the patient. Anticancer Drugs 2017;28:551–556.

50. Boisdron-Celle M, Capitain O, Faroux R et al. Prevention of 5-fluorouracil-induced early severe toxicity by pre-therapeutic dihydropyrimidine dehydrogenase deficiency screening: Assessment of a multiparametric approach. Semin Oncol 2017;44: 13–23.

51. Etienne-Grimaldi MC, Boyer JC, Beroud C et al. New advances in DPYD genotype and risk of severe toxicity under capecitabine. PLoS One 2017;12:e0175998.

52. Ruzzo A, Graziano F, Galli F et al. Dihydropyrimidine dehydrogenase pharmacogenetics for predicting fluoropyrimidine-related toxicity in the randomised, phase III adjuvant TOSCA trial in high-risk colon cancer patients. Br J Cancer 2017;117:1269–1277.

53. Vivaldi C, Arrigoni E, Morganti R et al. Analysis of DPYD and UGT1A1 genotype in patients with advanced pancreatic cancer treated with modified FOLFIRINOX. Ann Oncol. 2017;28(suppl 5):VI48.

54. Nahid NA, Apu MNH, Islam MR et al. DPYD*2A and MTHFR C677T predict toxicity and efficacy, respectively, in patients on chemotherapy with 5-fluorouracil for colorectal cancer. Cancer Chemother Pharmacol 2018;81:119–129.

55. Cremolini C, Del Re M, Antoniotti C et al. DPYD and UGT1A1 genotyping to predict adverse events during first-line FOLFIRI or FOLFOXIRI plus bevacizumab in metastatic colorectal cancer. Oncotarget 2018;9:7859–7866.

56. Amirfallah A, Kocal GC, Unal OU et al. DPYD, TYMS and MTHFR genes polymorphism frequencies in a series of Turkish colorectal cancer patients. J Pers Med. 2018;8:45.

57. Toffoli G, Innocenti F, Polesel J et al. The genotype for DPYD risk variants in patients with colorectal cancer and the related toxicity management costs in clinical practice. Clin Pharmacol Ther 2019;105:994–1002.

58. Alvarado Fernández M, Murillo Izquierdo M, Cordero Ramos J et al. 5PSQ-061 Determination of genetic polymorphisms of the dihydropyrimidine dehydrogenase gene in real clinical practice: Posological individualisation. Eur J Hosp Pharm 2019; 26(suppl 1):A229-A230.

59. Negarandeh R, Salehifar E, Saghafi F et al. Evaluation of adverse effects of chemotherapy regimens of 5-fluoropyrimidines derivatives and their association with DPYD polymorphisms in colorectal cancer patients. BMC Cancer 2020; 20:560.

60. National Cancer Institute. Common Terminology Criteria for Adverse Events v5.0. Atlanta, GA: National Cancer Institute, 2017. Available at https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf. Accessed January 2, 2020.

61. Amstutz U, Henricks LM, Offer SM et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for Dihydropyrimidine Dehydrogenase Genotype and Fluoropyrimidine Dosing: 2017 update. Clin Pharmacol Ther 2018; 103:210–216.

62. Lunenburg C, Henricks LM, Guchelaar HJ et al. Prospective DPYD genotyping to reduce the risk of fluoropyrimidine-induced severe toxicity: Ready for prime time. Eur J Cancer 2016;54:40–48.

63. Henricks LM, Opdam FL, Beijnen JH et al. DPYD genotype-guided dose individualization to improve patient safety of fluoropyrimidine therapy: Call for a drug label update. Ann Oncol 2017;28:2915–2922.

64. European Medicines Agency. 5-Fluorouracil (i.v.), capecitabine and tegafur containing products: Pre-treatment testing to identify DPD-deficient patients at increased risk of severe toxicity. European Medicines Agency Web site, 2020. Available at https://www.ema.europa.eu/en/medicines/dhpc/5-fluorouracil-iv-capecitabine-tegafur-containing-products-pre-treatment-testing-identify-dpd. Accessed February 11, 2021.

65. Ison G, Beaver JA, McGuinn WD, Jr. et al. FDA approval: Uridine triacetate for the treatment of patients following fluorouracil or capecitabine overdose or exhibiting early-onset severe toxicities following administration of these drugs. Clin Cancer Res 2016;22:4545–4549.

66. U.S. Food and Drug Administration. Table of pharmacogenetic associations. U.S. Food and Drug Administration Web site, 2021. Available at https://www.fda.gov/medical-devices/precision-medicine/table-pharmacogenetic-associations. Accessed July 11, 2021.

See http://www.TheOncologist.com for supplemental material available online.